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Authors

Murphy, Stephen K
Bruch, Achim
Dong, Vy M

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Substrate-Directed Hydroacylation: Rh-Catalyzed Coupling of Vinyl Phenols and Non-Chelating Aldehydes

Stephen K. Murphy, **Dr. Achim Bruch**, and **Dr. Vy M. Dong**
Department of Chemistry, University of California, Irvine, California, 92697-2025, USA and Department of Chemistry, University of Toronto, 80 St. George St., Toronto, Ontario, M5S 3H6 Canada

Vy M. Dong: dongv@uci.edu

Abstract

We report a protocol for branched-selective hydroacylation of vinylphenols with aryl, alkenyl and alkyl aldehydes. This cross-coupling yields α-aryl ketones that can be cyclized to benzofurans, and it enables access to eupomatenoid natural products in four steps or less from eugenol. Excellent reactivity and high levels of branched regioselectivity are obtained. We propose that aldehyde decarbonylation is overcome by using an anionic directing group on the olefin and a small bite-angle diphosphine ligand.

Keywords

Hydroacylation; Benzofurans; Branched selectivity; C–H activation; Rhodium catalysis

Substrate-directed hydroacylation enables the regioselective construction of ketones with high atom-economy.[1-3] By using a directing-group on the olefin component (for example, 1,5-dienes,[4] homoallylic sulfides,[5] allylic alcohols,[6] or homoallylic alcohols[7]), the linear-selectivity of Rh-catalyzed hydroacylation can be overturned to yield branched ketones.[8] However, most hydroacylation processes are limited by the need for chelating aldehydes, such as salicylaldehydes,[9] 2-aminobenzaldehydes,[10] β-sulfur aldehydes,[11] or 2-pyridylaldimines,[12] to facilitate C–H bond activation and suppress competitive decarbonylation. Developing new catalysts for the branched-selective hydroacylation of olefins with non-chelating aldehydes remains challenging. As alternatives to Rh-catalysis, Krische and Ryu applied Ru-hydrides for the branched-selective addition of non-chelating aldehydes to enones and 1,3-dienes.[13] Recently, Glorius reported an NHC-catalyzed method for efficient linear selective coupling of benzaldehydes and electron deficient styrenes.[14] Additionally, a few promising examples of branched-selective coupling with electron rich styrenes were reported albeit with low-to-moderate yields. In light of this challenging transformation, we hypothesized that an *anionic* directing group on the olefin could enable branched-selective hydroacylation with broad aldehyde scope (Scheme 1).

Correspondence to: Vy M. Dong, dongv@uci.edu.

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The choice of an anionic directing group allows the use of a neutral Rh catalyst, which is highly electron-rich compared to the commonly used cationic catalysts. Neutral Rh complexes, for example Milstein's $(Me_3P)_3RhCl$ complex and Brookhart's $Cp^*Rh(olefin)_2$ catalyst, are reactive towards non-directed aldehyde C–H bond activation.[15] On the basis of our double-chelating hydroacylations with salicylaldehydes,[5-7] we reasoned that an anionic group should promote olefin binding and guide formation of the branched ketone. To achieve this goal, we focused on using bidentate phosphines to make the acyl-Rh^{III}-hydride coordinatively saturated and therefore stable toward decarbonylation.[16]

In principle, a wide range of acidic functional groups could be used to generate the requisite anionic directing group in the presence of catalytic base. Due to the prevalence of phenols and their wide range of pK_a values, we chose vinylphenols as the olefin for initial studies (Scheme 2). Willis recently reported a method to access furans *via* alkyne hydroacylation, which relied on the coupling of β-sulfur aldehydes with propargylic alcohols.[17] In that case, the sulfide directing group was retained in all of the furan products. Here, the products of vinyl phenol hydroacylation can be cyclized to a wide variety of benzofurans, including biologically relevant eupomatenoids.

To test our hypothesis, we examined the coupling of hydrocinnamaldehyde with 4-chloro-2-vinylphenol in the presence of catalytic base, Rh, and various ligands (Table 1). We maintained a 2:1 P:Rh ratio to generate the proposed saturated acyl-Rh^{III}-hydride intermediate (Scheme 1). Both $P(OMe)_3$ and bis(diphenylphosphino)methane (dppm) were effective ligands and provided the branched product with >20:1 b:l selectivity (entries 1 and 2). Weller and Willis used similar small bite-angle diphosphines to achieve hydroacylation of alkenes and alkynes with β-sulfur substituted aldehydes, and they suggested that the small bite-angle promotes reductive elimination.[11e] A more sterically demanding and basic ligand, bis(dicyclohexylphosphino)methane (dcpm), provided a faster reaction rate and higher yield (entry 3, 99% yield). Diphosphines with larger bite-angles were completely ineffective, and the dearth of chiral small bite-angle diphosphines precluded an enantioselective process. Changing the solvent from 1,2-DCE to THF and increasing the vinylphenol concentration to 1 M further increased reaction rates. In line with Bergman's observation that Rh-alkoxide complexes undergo rapid exchange with phenols,[18] $[Rh(cod)OMe]_2$ is an effective catalyst in the absence of added base (entry 4, 99% yield). Conveniently, this protocol uses commercially available catalyst components, and unlike the cationic Rh diphosphine catalysts currently used for hydroacylation, does not require hydrogenation to activate the catalyst.

Aldehydes with diverse steric and electronic structures are excellent coupling partners (Table 2). Primary and secondary aliphatic aldehydes routinely transform to ketones with yields above 90% (entries 1-8), and acidic α-protons (entry 4) and potentially labile β-silyloxy groups (entry 5) are tolerated. Alkenyl aldehydes are traditionally challenging substrates in hydroacylation due to issues of chemoselectivity and their tendency to form π-complexes with Rh.[15c] Nonetheless, we report the first Rh-catalyzed hydroacylations using alkenyl aldehydes in the absence of an aldehyde directing group (entries 9-11). These substrates react at slightly elevated temperature and catalyst loading (100 °C, 4 mol % $[Rh(cod)OMe]_2$ and 8 mol % dcpm). Electron rich benzaldehydes (entries 12 and 13)

maintain the >20:1 b:l ratio observed for most other substrates, while electron-neutral and deficient variants give slightly lower but synthetically useful regioselectivities (entries 14 and 15). Vanillin was effectively transformed in 82% yield to its corresponding α-arylketone product (entry 16). This protocol encompasses one of the broadest aldehyde scopes reported for hydroacylation to date, highlighting the unique reactivity of neutral [Rh(X)(dcpm)] fragments towards activating aldehyde C–H bonds.

Vinylphenols with highly varied pK_a's (Table 3) couple with hydrocinnamaldehyde in 50-93% yields and >20:1 b:l regioselectivity (entries 1-4). Sterically demanding vinylphenols are suitable substrates (entries 5-7), but the 6-Me substrate gives only 11% yield due to competitive aldol condensation. We predicted a concentration-dependent chemoselectivity for aldol condensation and hydroacylation due to the strong binding of the vinyl phenol to Rh. In line with this hypothesis, we observed an increased yield of 50% upon diluting the reaction by five-fold. Disubstituted vinyl phenols (2-propenylphenol) and further homologated substrates (2-allylphenol) were unreactive with hydrocinnamaldehyde. Secondary aldehydes generally provide higher yields than primary aldehydes, presumably because they are resistant to aldol condensation (entries 8-11, 74-95% yields). These bulkier substrates exhibit slightly diminished regioselectivity with electron rich vinylphenols. The third substrate class, alkenyl aldehydes, gives almost identical results to hydrocinnamaldehyde (entries 12-15). Transformations with benzaldehyde display varied regioselectivities (from 9:1 to >20:1) depending on the electronics of the vinylphenol (entries 16-20). Sterically demanding olefins, including a bulky 4,6-(*t*-Bu)$_2$ substituted vinylphenol are excellent coupling partners for benzaldehyde (entries 18-20).

This method provides an alternative approach to orthosubstituted α-aryl ketones, which are typically difficult to access by traditional ketone α-arylation.[19] The products of this directed olefin hydroacylation can be further elaborated in a straight forward manner. For example, the phenol component can be triflated and engaged in Suzuki-Miyaura cross coupling (Figure 1, eq 1).[20] Alternatively, treatment of the resulting ketones with trifluoroacetic acid (TFA) induces cyclocondensation to the corresponding benzofurans in quantitative yields (Figure 1, eq 2).[21]

Considering this benzofuran synthesis, we targeted the eupomatenoid class of neolignans, (Table 4) which exhibit insecticidal, antimicrobial, antioxidant, and antitumor activity.[22] Most recent syntheses of these compounds establish the benzofuran core first and rely on either Stille or Kumada coupling to append propenyl or allyl units.[23] In contrast, we derived a fully functionalized vinylphenol from eugenol and used hydroacylation and cyclocondensation to forge the benzofuran core. These coupling partners are highly reactive and allow hydroacylation to occur at moderate temperatures of 70–80 °C. Our approach enables three-step syntheses of eupomatenoids 17 and 18, and four-step syntheses of eupomatenoids 12 and 16. The olefin proximal to the phenol reacts chemoselectively in the presence of distal allyl and propenyl units (depicted as R^2).

In summary, we have developed a catalyst system for branched selective hydroacylation of olefins bearing anionic directing groups with a wide range of aryl, alkenyl, and alkyl aldehydes. High branched selectivity and high reactivity were generally observed. In

combination with a cyclocondensation, we applied this method to access several neolignan natural products. Based on this work, we expect that other acidic functional groups (e.g. anilines, sulfonamides, hydroxyl groups, or carboxylic acids) can be used to generate anionic directing groups *in situ* and further expand the applications of hydroacylation. Given the mild reaction conditions, neutral [Rh(X)(dcpm)] fragments are highly reactive towards aldehyde C–H bond activation and hold promise for future hydroacylations with non-chelating aldehydes. A detailed mechanistic study is underway to elucidate the factors leading to this high reactivity and selectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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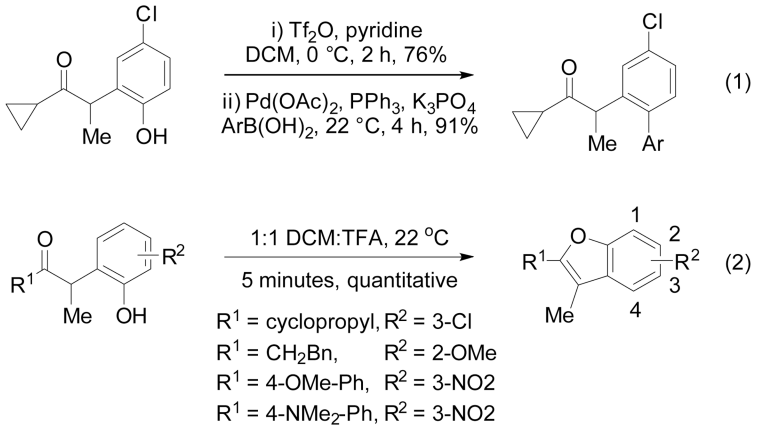
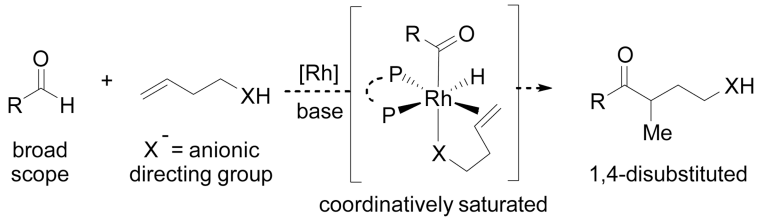
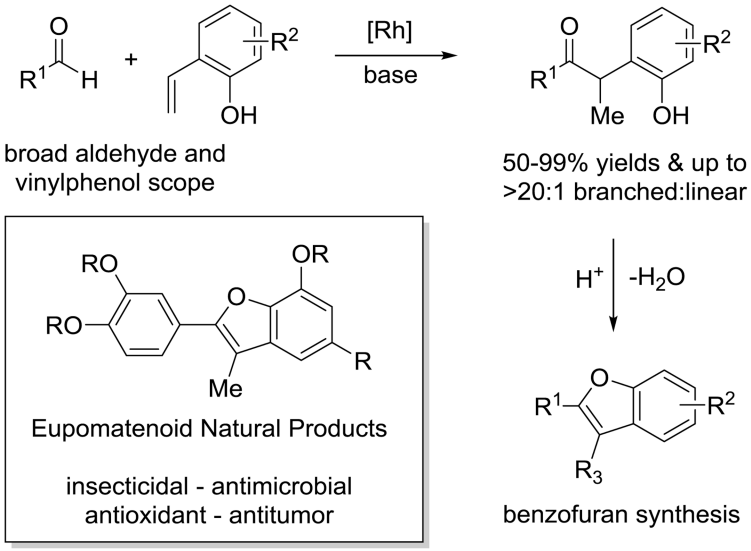


Figure 1.
Derivatization of hydroacylation products (Ar = 4-methoxyphenyl).



Scheme 1.

Proposed regioselective hydroacylation of olefins bearing an anionic directing group.

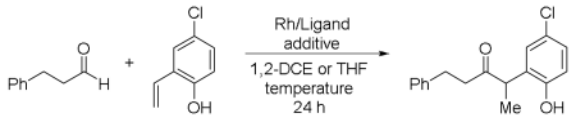


Scheme 2.

Hydroacylation of vinyl phenols with alkyl, alkenyl, and aryl aldehydes.

Table 1

Optimization of reaction conditions.[a]



#	Rh	Ligand	Additive	*T* [°C]	Yield [%]
1[b]	$[Rh(cod)Cl]_2$	$P(OMe)_3$	K_3PO_4	80	75
2[c]	$[Rh(cod)Cl]_2$	dppm	K_3PO_4	60	90
3[c]	$[Rh(cod)Cl]_2$	dcpm	K_3PO_4	60	99
4[d]	$[Rh(cod)OMe]_2$	dcpm	none	60	99

[a] b:l ratios were >20:1 in all cases as determined by NMR analysis of the crude reaction mixtures.

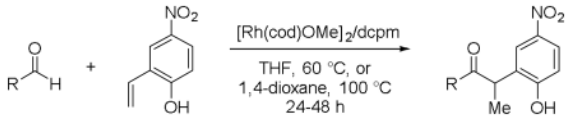
[b] 5 mol % Rh dimer, 20 mol % ligand, 10 mol % K_3PO_4, 1,2-DCE solvent, 0.4 M in vinyl phenol.

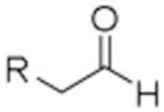
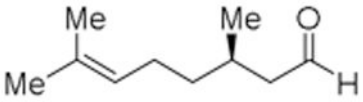
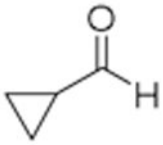
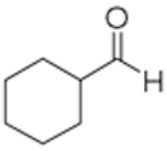
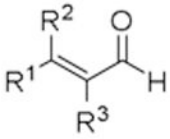
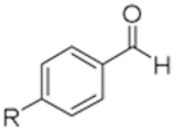
[c] 2.5 mol % Rh dimer, 5 mol % ligand, 10 mol % K_3PO_4, 1,2-DCE solvent, 0.4 M in vinyl phenol.

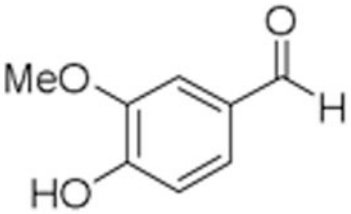
[d] 2 mol % Rh dimer, 4 mol % ligand, THF solvent, 1 M in vinyl phenol.

Table 2

Aldehyde scope.[*a,b*]



#	Aldehyde		Yield [%]	b:l
1		R = Bn	96	>20:1
2		Bu	99	>20:1
3		^{i}Pr	91	>20:1
4		Ph	98	>20:1
5		CH_2-OTBS	68	>20:1
6[*c*]			99	>20:1
7			94	>20:1
8			91	>20:1
9		R^1 = Ph; R^2, R^3 = H	95	>20:1
10		R^1, R^2 = Me, R^3 = H	62	10:1
11		R^1, R^2 = H, R^3 = Me	31	>20:1
12		R = NMe_2	77	>20:1
13		R = OMe	79	>20:1
14		R = H	78	16:1
15		R = CO_2Me	94	12:1

#	Aldehyde	Yield [%]	b:l
16		82	19:1

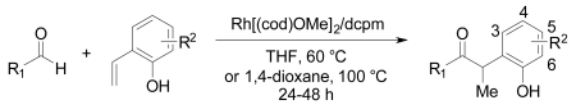
[a] b:l ratios were determined by NMR analysis of the crude reaction mixtures.

[b] Alkyl aldehydes: 2 mol % $[Rh(cod)OMe]_2$ and 4 mol % dcpm, THF, 60 °C. Alkenyl and aryl aldehydes: 4 mol % $[Rh(cod)OMe]_2$ and 8 mol % dcpm, 1,4-dioxane, 100 °C. All reactions were carried out at 1 M with respect to vinylphenol.

[c] 1:1 d.r.

Table 3

Olefin scope.[a,b]



#	Product	R^2	Yield [%]	b:l
1		6-OMe	80	>20:1
2		5-OMe	50	>20:1
3		4-OMe	55	>20:1
4		4-F	93	>20:1
5	(R^1 = $BnCH_2$)	6-Me	11 (50[c])	>20:1
6		3-Me	93	>20:1
7		4,6-(t-Bu)$_2$	67	>20:1
8		6-OMe	93	11:1
9		4-OMe	74	10:1
10		6-Me	91	>20:1
11	(R^1 = Cy)	3-Me	95	>20:1
12		6-OMe	92	>20:1
13		4-OMe	52	>20:1
14		6-Me	62	>20:1
15	(R^1 = $PhCHCH_2$)	3-Me	96	>20:1
16		6-OMe	88	19:1
17		4-OMe	53	9:1
18		6-Me	81	>20:1
19		3-Me	77	>20:1
20	(R^1 = Ph)	4,6-(t-Bu)$_2$	84	>20:1

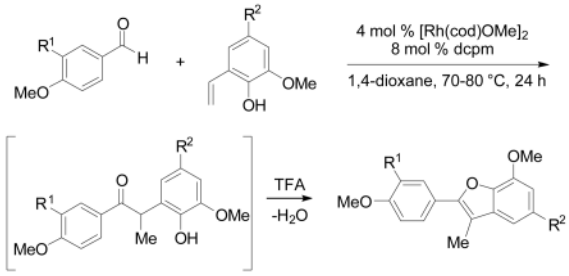
[a] b:l ratios were determined by NMR analysis of the crude reaction mixtures.

[b] Alkyl aldehydes: 2 mol % $[Rh(cod)OMe]_2$ and 4 mol % dcpm, THF, 60 °C. Alkenyl and aryl aldehydes: 4 mol % $[Rh(cod)OMe]_2$ and 8 mol % dcpm, 1,4-dioxane, 100 °C. All reactions were carried out at 1 M with respect to vinylphenol unless otherwise noted.

[c] 0.2 M with respect to vinylphenol.

Table 4

Eupomatenoid natural product synthesis.



#	Name	R^1	R^2	*T* [°C]	Yield [%]
1	eupomatenoid 12	OMe	1-propenyl	80	70
2	eupomatenoid 16	H	1-propenyl	80	80
3	eupomatenoid 17	H	allyl	70	78
4	eupomatenoid 18	OMe	allyl	70	82